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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/517,717 | 03/17/2005 | Terrence R. Burke JR. | 231461 | 5693 |

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| EXAMINER | |
|---|---|
| KOSAR, ANDREW D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1654 | |

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| 11/21/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/517,717 | BURKE ET AL. | |
| | Examiner | Art Unit | |
| | Andrew D. Kosar | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *81-87 and 90-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81-87 and 90-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *10 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/10/04,12/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election, filed January 29, 2007, is acknowledged. Upon review of the prior art and the parent Application history, the examiner has concluded that the restriction requirement may be withdrawn. Thus, the restriction requirement mailed January 11, 2007 is herein withdrawn.

Claims 81-87 and 90-97 are pending and have been examined on the merits.

### *Specification*

The disclosure is objected to because of the following informalities:

The chemical structure for compound 233 is absent from page 14 of the disclosure, however it is present in the priority document 60/392,028 on page 14.

Appropriate correction is required.

Please note, the lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Claims 86, 92 and 96** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating breast cancer in a mammal with the claimed compounds, does not reasonably provide enablement for treating or preventing any 'disease, state or condition'. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

*(1) The nature of the invention and (2) the breadth of the claims:*

The claims are drawn to methods of treating or preventing a disease, state or condition via administration of a compound of claim 81, 82 or 83. Given their broadest interpretation, the claims are drawn to the prevention of <u>any</u> disease, state, or condition. The claims are discussed herein with regards to the subgenus 'cancer' within the genus of 'all diseases, states, or conditions'. Further, the claims do not specifically define the patient population as "in need thereof," and thus the claims imply the method can be practiced in any mammal.

With regards to the patient population, Applicant is suggested to amend the claims to identify the patient population is 'in need thereof,' to distinguish from administration to any mammal.

*(3) The state of the prior art and (4) the predictability or unpredictability of the art:*

he state of the art in curing cancer in humans is unpredictable, as stated by Dr. Richard Klausner (*in* C. Gorman, PTO-892), "We have cured mice of cancer for decades – and it simply didn't work in people." (Page 1) Further, the state of the art with angiogenesis inhibitors is unpredictable, as stated in the same article, "Nor will angiogenesis inhibitors work equally well against all cancers." (Page 3).

With regards to tumors implanted under the skin in mouse models, "[m]ice distort or exaggerate what you see in humans," according to Robert Kerbel (Page 8), because they "grow much more rapidly than deep-seated human tumors." (Page 8). Further, it is stated that, "rodents are better predictors of human reaction to cardiovascular or anti-inflammatory agents than to cancer or diseases of the central nervous system." (Page 8). The article states that J. Michael Bishop, "...is breeding mice to provide better models for studying leukemia..." (Page 8) and that the similarity between mouse and man "is still a legitimate issue." (Page 8).

Additionally, with regards to *in vivo* models, GURA (T. Gura, PTO-892) states, "Pharmaceutical companies often test drug candidates in animals carrying transplanted human tumors, a model called a xenograft. But not only have very few of the drugs that showed anticancer activity in xenografts made it into the clinic, a recent study...suggests that the xenograft model missed effective drugs. The animals apparently do not handle the drugs exactly the way the human body does," (Page 1041) and with regards to xenograft models, "tumors don't behave like naturally occurring tumors in humans – they don't spread to other tissues, for example. Thus, drugs tested in the xenografts appeared effective but worked poorly in humans."

(Page 1041). Further it is stated that they, "had basically discovered compounds that were good mouse drugs rather than good human drugs" (Page 1041).

With regards to *in vitro* models, DERMER (G.B. Dermer, PTO-892) teaches that the model systems cell lines for cancer are "unsuitable for the job". He states that the "Petri dish cancer is a really poor representation of malignancy, with characteristics profoundly different from the human disease."

Further, with regards to *in vitro* models, McKIE (R. McKie, PTO-892) states that, "Hundreds of cancer research projects have produced worthless or misleading results because the scientists have been using incorrectly identified samples." (Page 1), estimated to be, "up to 1/3 of the cell lines" (Page 2), and that, "Hundreds of research papers on these cell lines have already been published, however, and most of their conclusions are invalid, say experts." (Page 3).

Alan Oliff states in Gura that, "[t]he fundamental problem in drug discover for cancer is that the model systems are not predictive at all." (Page 1041).

Since the models systems are highly unpredictable for treating cancer and determining effective compounds remains largely unsolved, means for treating or preventing all forms of cancer is highly unpredictable.

Further, it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes) – including preventing such disorders as AIDS/HIV or cancer, which are clearly not recognized in the medical art as being totally preventable conditions.

*(5) The relative skill of those in the art:*

In view of the art above, the level of skill in the art is low, particularly with regards to treating or preventing "any disease, state or condition."

*(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:*

Applicants have reasonably demonstrated and/or disclosed that the specific compounds are useful as a therapeutic agent for treating breast cancer through an *in vitro* model. However, the claims also encompass using the claimed compound to prevent any disease, state, or condition, which is clearly beyond the scope of the instantly disclosed/claimed invention. Please note that the term "prevent" is an absolute definition which means to stop from occurring and, thus, requires a higher standard for enablement than does "therapeutic" or "treat", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes) – including preventing such disorders as AIDS/HIV or cancer, which are clearly not recognized in the medical art as being totally preventable conditions.

Further, the specification is silent to any of the instantly claimed compositions being used for treating other forms of cancer, alone or in combination with another compound, in any model system in vitro *or* in vivo, and additionally lacks any discussion or evidence that the disclosed model is accepted, or acknowledged, as a predictive model for any other disease, condition or state.

*(8) The quantity of experimentation necessary*:

Considering the state of the art as discussed by the references above, particularly with regards to *in vitro* and *in vivo* models of cancer and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

***Double Patenting***

**Claims 81-87 and 90-97** are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-47 of U.S. Patent No. 6,977,241 B2 in view of BOTTARO (WO 01/28577 A2, PTO-1449).

With regards to the applicability of Bottaro, the examiner finds support for the generic claim 82 in the parent Application and priority document, and thus is afforded the priority date of the Provisional Application 60/226,671. However, the specific species does not find support in the parent document (now US Patent 6,977,241 B2), and has been afforded the priority date of Provisional Application 60/392,028. Thus, Bottaro is available as prior art, with respect to selection of the dicarboxymethyl moiety.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant compounds of claim 81 and 83 are embodied in the generic claim of '241, and while a species is not necessarily anticipated by a genus, the core structure of the instant claims is embodied in at least claims 18 and 20, such that one would at once envisage that the instantly claimed compounds are embodied by the claims of '241. Further, with regards to the phosphomimetic compound ($R_2$ is dicarboxymethyl as in instant claim 83),

dicarboxyalkyl$_{C(1-6)}$ is specifically embodied as a species of $R_2$ in '241, and Bottaro teaches dicarboxymethyl phosphomimetics sharing a significant structural similarity to the instant compounds, such that one would have been motivated to have selected the dicarboxymethyl mimetic for incorporation with the expectation that it would enhance the activity of the compound as taught in Bottaro.

**Claims 81-87 and 90-97** are directed to an invention not patentably distinct from claims 1-47 of commonly assigned US Patent 6,977,241 B2, for the reasons set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US Patent 6,977,241 B2, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Andrew D Kosar
Patent Examiner
Art Unit 1654